REMARKS

Prior to this amendment, claims 1, 5-8, 10-26, 30, 34, 35, and 43 were pending in this application. By this amendment, new claims 44-46 are added. New claim 44 is supported at least by page 24, line 21 in the specification. New claims 45 and 46 are supported at least by page 25, lines 23-30 in the specification.

REJECTIONS UNDER § 112

In response to the rejection of claim 5 for lack of antecedent basis, claim 5 is amended to recite "growth factor" instead of "biological material." Accordingly, withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER § 103

The Office Action rejects claims 1 and 35, and various claims that depend therefrom, under § 103(a) as being obvious over Naughton (US 5,830,708) in view of Mitchell (US 2002/00115208), Patel (US 7,087,089), Wolff (WO 99/55379), Herlyn (WO 98/39035), and/or Schwarz (US 6,656,916). Applicants respectfully request reconsideration of these rejections.

In the method of claims 1 and 35, the body tissue of a primate or domesticated animal is conditioned (e.g., by gene transfection) *in vivo* to increase the production of a growth factor. The body tissue is harvested and decellularized to obtain an extracellular matrix material containing the growth factor. The decellularization process involves the use of a protease inhibitor.

Naughton describes methods for producing extracellular matrix material by culturing extracellular matrix-secreting human stromal cells on a biocompatible three-dimensional framework *in vitro*. (See, e.g., Abstract). After secretion of the extracellular matrix onto the framework, the stromal cells are killed, and the cells and cellular contents are removed from the framework. (Naughton, at Abstract). As conceded by the Office Action, Naughton does not teach the step of conditioning body tissue of a donor animal *in vivo*. Rather, Naughton cultures and conditions tissue *in vitro*. Thus, the Office Action combines Naughton with Mitchell for its teaching of *in vivo* culturing as an alternate to culturing tissue *in vitro*.

Mitchell describes methods for producing tissue engineered constructs by growing cells *in vitro* on a substrate and then decellularizing the construct to produce a decellularized construct consisting largely of extracellular matrix components. (See, e.g., Abstract). A substrate is seeded

with cells and as the cells grow, they secrete extracellular matrix protein (such as collagen and elastin) onto the substrate. (Mitchell, at col. 8, lns. 28-33). Mechanical, electrical, or chemical stimuli can be applied to the cells to stimulate the development of desired properties. (Mitchell, at col. 8, lns. 39-41). Because the method of Mitchell relies on the use of an artificial substrate for seeding of the cells, "production of the tissue engineered construct involves culturing the developing tissue *primarily* in vitro." (Mitchell, at col. 8, lns. 46-48; emphasis added). However, while indicating that the method is "*primarily* in vitro," Mitchell mentions briefly in passing that "culturing the tissue in vivo are also within the scope of the invention." (Mitchell, at col. 8, lns. 46-48).

Its method being primarily applicable to *in vitro* culturing, Mitchell provides guidance on how the *in vitro* culturing should be done, including the shape and composition of the artificial substrate (col. 12, ln. 35 – col. 13, ln. 15), the different cell types that can be used to seed the substrate (col. 13, lns. 16-45), how the substrate should be seeded (col. 14, lns. 33-48), the quantity of cells needed to seed the substrate (col. 14, lns. 37-41), the type of culture media that should be used (col. 15, lns. 15-27), and the culture conditions that need to be controlled (col. 15, lns. 31-35). In contrast, Mitchell provides no specific information about how *in vivo* culturing and/or conditioning should be performed.

Summary of arguments in prior response

The claimed method is more than simply the combination of just any conditioning process, for increasing just any biologic material in the extracellular matrix, with just any decellularizing process. In the claimed method, there is a synergistic, functional relationship between the growth factor, the extracellular matrix, and the decellularizing step using a protease inhibitor that work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

MPEP 2141.02 instructs that a proper obviousness analysis requires a determination of "whether the claimed invention *as a whole* would have been obvious," rather than simply determining the differences between the prior art and the claims. Thus, it is improper to argue that a claim is obvious simply because each element of the claim, taken by themselves, can be found somewhere in the prior art. Applicants respectfully submit that the claimed method, as a whole, is not appreciated or suggested by the cited references.

In the claimed method, the conditioning step is for increasing the quantity of growth factors in the extracellular matrix. There is a functional relationship between these two elements of the conditioning step because the extracellular matrix can serve as a local depot for the storage of growth factors. *See, e.g.*, Taipale et al., "Growth factors in the extracellular matrix," FASEB Journal, vol. 11 (1997) (previously submitted). As such, the extracellular matrix material of the present invention can provide a rapid release of growth factors into the local environment (e.g., into a wound) without the need for the time-consuming process of *de novo* protein synthesis. Thus, because the extracellular matrix can serve as a storage depot for growth factors, there is a special functional relationship in the claimed method between the growth factor and the extracellular matrix, which work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

Moreover, the decellularizing step using a protease inhibitor works in conjunction with the increased growth factors present in the extracellular matrix. In general, these growth factors are attached to the extracellular matrix by protease-sensitive bonds. It is the proteolysis of these bonds that allows for the rapid release of the growth factors into the local environment. Therefore, during the decellularization step, proteases released from lysed or disrupted cells may cause the unwanted, premature release of the growth factors from the extracellular matrix. As a result, the growth factors would be lost from the extracellular matrix and the work performed in conditioning the body tissue to increase growth factor production would be negated. In the claimed method, the use of a protease inhibitor in the decellularizing step plays the important role of preserving the increased growth factors produced in the conditioning step.

Thus, the invention of claims 1 and 35 is more than just the sum of its parts. There is a special functional relationship between the growth factor, the extracellular matrix, and the decellularizing step using a protease inhibitor that work synergistically together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

Additional arguments

As further evidence that the claimed invention, as a whole, is more than just the sum of its parts, Applicants submit that the art has come to recognize that the three-dimensional organization of the growth factors in *in vivo*-derived extracellular matrix results in superior

performance compared to extracellular matrix derived from *in vitro* culturing. Applicants refer to the report by Badylak ("Xenogeneic extracellular matrix as a scaffold for tissue reconstruction," Transplant Immunology, 2004, vol. 12:367-377), which is attached hereto. Badylak was published in 2004 (*after* the filing date of the present application) and demonstrates that the three-dimensional organization of the growth factors that results from the claimed invention provides an advantage that was not appreciated until after the date of the invention.

Badylak discusses the use of bioscaffolds derived from xenogeneic (from another species) extracellular matrix. In regards to bioscaffolds made from native tissue, Badylak reports as follows:

> The composition of these bioscaffolds includes the structural and functional proteins that are part of *native* mammalian extracellular matrix. The three-dimensional organization of these molecules *distinguishes ECM scaffolds from synthetic scaffold materials* and is associated with constructive tissue remodeling instead of scar tissue.

(Badylak, at Abstract; emphasis added). Badylak further states as follows:

> An important characteristic of the intact ECM that distinguishes it from other scaffolds for tissue reconstruction is its diversity of structural and functional proteins. The bioactive molecules that reside within the ECM and their unique *spatial distribution* provide a reservoir of biologic signals.
> . . .
> An advantage of utilizing the ECM in its native state as a substrate or scaffold for cell growth and differentiation is the presence of *all the attendant growth factors* (and their inhibitors) in the same relative amounts that exist in nature and perhaps more importantly, in their *native three-dimensional ultrastructure.*

(Badylak, at pg. 369, beginning at left column, third paragraph; emphasis added).

With regards to the meaning of "native," Applicants refer to the cited Mitchell reference, which defines "native tissue" as tissue that is harvested from an animal or human and that remains substantially intact and substantially retains the structure in which it is naturally found within the body of the animal or human. (Mitchell, at col. 6, lns. 61-65). Thus, according to Badylak, extracellular matrix derived from *native* tissue harvested from an animal is distinguished from synthetic scaffolding materials (such as those made using *in vitro* techniques) by the growth factors being present in their "native three-dimensional ultrastructure."

Applicants submit that there is a nexus between the particular combination of features in the claimed invention and what Badylak recognizes to be the particular characteristics of native

extracellular matrix that gives it superior performance over synthetic scaffolding materials. The claimed invention uses "body tissue of a donor animal" (i.e., native tissue). The claimed invention also uses *in vivo* conditioning of the body tissue to increase the production of growth factors. The claimed invention also uses a protease inhibitor in the decellularizing step to, as explained above, protect the growth factors from premature release.

Badylak demonstrates that the result obtained by the claimed invention is more than simply the sum of its parts. There is a special functional relationship between the growth factor, the body tissue-derived extracellular matrix, and the decellularizing step using a protease inhibitor that work synergistically together in a manner that was unappreciated by the art at the time of the claimed invention.

For at least these reasons, Applicants respectfully submit that claims 1 and 35, and the claims that depend therefrom, are non-obvious over the cited references. Accordingly, withdrawal of the rejections is respectfully requested.

INFORMATION DISCLOSURE STATEMENT

By the telephone call with the Examiner on June 8, 2010 regarding the lined-through references on the IDS submitted on 7/21/2009, Applicants understand that the Examiner has received and considered these references, but these references were lined-through because of improper citation format.

CONCLUSION

Applicant(s) respectfully submit that the present application is in condition for allowance. The Examiner is invited to contact Applicant(s)' representative to discuss any issue that would expedite allowance of this application.

The Commissioner is authorized to charge all required fees, fees under § 1.17, or all required extension of time fees, or to credit any overpayment to Deposit Account No. 11-0600 (Kenyon & Kenyon LLP).

Respectfully submitted,

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